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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/790,540	01/30/97	HUSE W	P-IX-2405

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EXAMINER	
GAMBEL, P	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 06/09/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/780,640	Huse
Examiner	**Group Art Unit**
GAMBEL	1642

☒ Responsive to communication(s) filed on *Mar 6, 1998*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-25* is/are pending in the application.

Of the above, claim(s) *19-25* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-18* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group Art Unit 1642.

2. Applicant's amendment, filed 3/6/98 (Paper No. 7), is acknowledged.
Claim 1 is amended.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 3/6/98 (Paper No. 7).
The rejections of record can be found in the previous Office Action (Paper No. 5).

4. Applicant's election with traverse of Group I in Paper No. 7 is acknowledged. The traversal is on the ground(s) that it would not be an undue burden upon the examiner. This is not found persuasive because of the reasons of record set forth in Paper No. 4). Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case, the products of Group I as claimed can be used in a materially different process such as immunopurification procedures or detection/diagnostic assays. Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II and Groups I and II have acquired a separate status in the art as shown by their different classification and divergent subject matter, restriction for examination purposes as indicated is proper
The requirement is still deemed proper and is maintained.

Claims 19-25 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.
Claims 1-18 are under consideration.

5. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 5. Applicant is reminded to amend the specification to correspond to how the figures will be corrected

6. Claims 1- 18 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-48 of copending application USSN 08/790,540. Although the conflicting claims are not identical, they are not patentably distinct from each other because each application is drawn to the same or nearly the same vitaxin-specific antibodies and nucleic acid encoding said antibodies and modifications thereof.
This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-18 are directed to an invention not patentably distinct from claims 1-48 of commonly assigned USSN 08/790,540.

Commonly assigned USSN 08/790,540, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78© to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

Applicant's amendment, filed 3/6/98 (Paper No. 7), indicates that the provisional grounds of rejection be deferred until there is an indication of allowable subject mater.

7. Claims 1-18 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention

Applicant's arguments, filed 3/6/98 (Paper No. 7), have been fully considered but are not found convincing essentially for the reasons of record set forth in the last Office Action (Paper No. 5).

Applicant submits that the terms "substantially the same" and functional fragment thereof" are clear to the skilled artisan in view of the specification. Applicant relies upon pages 14-15 of the instant specification to indicate that "substantially the same" encompasses a considerable degree, amount of or extent of sequence identity when compared to a reference sequence. Here, a nucleotide or amino acid sequence which is substantially the same as a heavy or light chain of LM609 or LM609 grafted antibody is a sequence which exhibits characteristics that are recognizable as encoding or being the amino acid sequence of LM609 or a LM609 grafted antibody, including minor modifications.

However, as applicant acknowledges, such phrases or terms encompass a considerable degree of modifications. In addition, applicant asserts reliance upon recognizable characteristics without defining the metes and bounds of said recognizable characteristics (e.g. structural and/or functional). While applicant argues $\alpha_v\beta_3$ binding activity or binding specificity in reference to the claimed antibodies, the claimed limitations are drawn to selective binding affinity to $\alpha_v\beta_3$. Again, the metes and bounds of "substantially the same" and functional fragment thereof" are ambiguous and unclear in the context of the claimed limitation versus applicant's asserted limitations of binding specificity and inhibitory activity. It is noted that the rejection of "functional fragments" per se would be obviated with the appropriate functional language set forth in the claims. However, the recitation of the "substantially the same" and "functional fragments thereof" retains issues under 35 USC 112, first and second paragraph. Applicant argues that the claimed invention encompasses only those LM609 grafted antibodies having substantially the same heavy and light chain CDR amino acid sequences as found in LM609 and exhibiting $\alpha_v\beta_3$ binding specificity but is not dependent on a particular percentage of sequence identity as defined by a

mathematical algorithm. Applicant asserts that once the sequence becomes sufficiently divergent that binding specificity to $\alpha_v\beta_3$ is no longer exhibited, the sequences can no longer be considered substantially the same. For the reasons of record and reiterated herein in part, applicant is invited to amend the claims to recite clearly the specificity and the functionality of the claimed antibodies, rather than relying and arguing the current claimed limitations. The terms and phrases are not defined by the claims, the specification does not provide a sufficient standard for ascertaining the requisite degree or metes and bounds of the claimed "phrases" above in the absence of a clear recitation of specificity and function and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. While the claims are read in light of the specification, limitations from the specification are not read into the claims.

Applicant's arguments are not found persuasive, particularly as it applies to the recitation of "substantially the same".

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

8. Upon reconsideration of applicant's arguments, filed 3/6/98 (Paper No. 7), in conjunction with the available sequence information, the previous requirement of the LM 609 antibody under 35 USC 112, first paragraph, has been withdrawn.

9. Claims 1-18 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Upon reconsideration of applicant's arguments, filed 3/6/98 (Paper No. 7), that the claims recite descriptive and distinguishing characteristics of the grafted antibodies, the previous rejection with respect to the recitation of "LM609" has been withdrawn.

B) Claims 1-18 are indefinite in the recitation of "grafted" because the metes and bounds of said term or the defining structural features are unclear. "Grafted" antibodies is a broad term that encompass any number of recombinant forms of antibodies and applicant has not provided sufficient direction to define said "grafted" forms.

Applicant's arguments, filed 3/6/98 (Paper No. 7), have been fully considered but are not found convincing for the reasons of record. In contrast to applicant's assertions, "grafted" is not an art recognized term. Rather "CDR-grafted" is the art recognized term or phrase. Amending the claims to "CDR-grafted", which appears to be the intention of applicant's claims and arguments, would obviate the rejection, provided no new matter is added. Again applicant is reminded that the claims are read in light of the specification, but limitations from the specification are not into the claims.

C) The amendments must be supported by the specification so as not to add any new matter.

10. An issue of public use or on sale activity has been raised in this application. In order for the examiner to properly consider patentability of the claimed invention under 35 U.S.C. 102(b), additional information regarding this issue is required as follows:

Biotechnology Newswatch (1/16/95 and 2/6/95) disclose the use of LM609 antibody including the humanized version of said antibody. Also it is noted that Cheresh, who developed the LM609 antibody and who conducted the in vivo experiments, is not listed as an inventor.

Applicant is reminded that failure to fully respond to this requirement for information will result in a holding of abandonment.

Applicant's arguments, filed 3/6/98 (Paper No. 7), have been fully considered but are not found convincing for the reasons of record set forth in Paper No. 5. Applicant asserts that cited articles are press releases describing the results obtained with a mouse monoclonal antibody and continued development of a grafted LM609 antibody and, in turn, do not constitute a public use of sale of a LM609 grafted antibody.

In contrast to applicant's assertions, Biotechnology Newswatch (1/16/95) clearly states that Scripps has licensed the rights to modify the antibody and to use it in treating angiogenesis to a Ixsys, Inc. and that the company has developed a humanized version of the LM609 antibody and was producing it for FDA studies. Further the company was seeking a corporate partner to develop the agent. Also, Biotechnology Newswatch (2/6/95) clearly states that Ixsys, Inc. and Celltech Biologics entered into an agreement to manufacture humanized LM609/Vitaxin. Applicant's assertions do not set forth facts to obviate the clear evidence that the humanized LM609 antibody (or Vitaxin) was made and used by others without apparent obligation or secrecy or restriction and that contracts and commercial exploitation of said humanized LM609 antibody (Vitaxin) were made more than one year prior to applicant's priority date. Further, this information was sufficiently informing to the public of humanizing the LM609, encompassed by the claimed invention. Given the absence of factual circumstances surrounding the activity and how these comport with the policies underlying the "on sale" and "public use" bars, the rejection is maintained. See MPEP 2133.03.

Applicant's arguments are not found persuasive.

11. Claims 1, 15-18 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Brooks et al. (Cell, 1994; 1449) for the reasons of record set forth in Paper No. 5.

Applicant's arguments, filed 3/6/98 (Paper No. 7), have been fully considered but are not found convincing for the reasons of record set forth in Paper No. 5. Applicant argues that the claimed compositions are directed to LM609 grafted antibodies in contrast to the prior art teachings of LM609 antibody. However, applicant's specification and arguments, filed in Paper No. 6, also indicate that "Substantially the same" encompasses LM609 or LM609 grafted antibody. Given the breadth of the claims to read on the LM609 antibody, applicant's arguments are not found persuasive. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention.

12. Claims 1, 15-18 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Choi et al. (J. Vasc. Surg., 1994; 1449) for the reasons of record set forth in Paper No. 5.

Applicant's arguments, filed 3/6/98 (Paper No. 7), have been fully considered but are not found convincing for the reasons of record set forth in Paper No. 4. Applicant argues that the claimed compositions are directed to LM609 grafted antibodies in contrast to the prior art teachings of LM609 antibody. However, applicant's specification and arguments, filed in Paper No. 6, also indicate that "substantially the same" encompasses LM609 or LM609 grafted antibody. Given the breadth of the claims to read on the LM609 antibody, applicant's arguments are not found persuasive. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention.

13. Claims 1, 15-18 stand rejected under 35 U.S.C. § 102(a)(e) as being anticipated by Kim et al. (U.S. Patent No. 5,578,704) for the reasons of record set forth in Paper No. 5.

Applicant's arguments, filed 3/6/98 (Paper No. 7), have been fully considered but are not found convincing for the reasons of record set forth in Paper No. 5. Applicant argues that the claimed compositions are directed to LM609 grafted antibodies in contrast to the prior art teachings of LM609 antibody. However, applicant's specification and arguments, filed in Paper No. 6, also indicate that "Substantially the same" encompasses LM609 or LM609 grafted antibody. Given the breadth of the claims to read on the LM609 antibody, applicant's arguments are not found persuasive. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention.

14. Claims 1-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Brooks et al. (Cell, 1994; 1449) or Choi et al. (J. Vasc. Surg., 1994; 1449) or Kim et al. (U.S. Patent No. 5,578,704) in view of art known gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof, as disclosed on pages 10-39 or Examples I and II of the instant specification or as cited by references on the 1449 for the reasons of record set forth in Paper No. 5.

Applicant's arguments, filed 3/6/98 (Paper No. 7), have been fully considered but are not found convincing for the reasons of record set forth in Paper No. 5. Applicant acknowledges that the prior art teach the LM609 antibody and its ability to inhibit $\alpha_v\beta_3$, but do not teach the nucleotide sequences encoding LM609 or LM609 grafted antibodies. Applicant's reliance on In re Deuel, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995) is acknowledged.

This proposition that the references failed to teach the structure of the claimed antibody precludes the teachings thereof from serving as evidence to establish a prima facie case of obviousness is contrary to a body of law which holds that a product may be described by the process of making it. As pointed in Ex parte Goldgaber, 41 USPQ2d 1173, 1176 (BPAI 1996), there is nothing intrinsically wrong in the application of methodology in the rejection product claims under 35 USC 103 depending on the particular facts of the case, the manner and context in which methodology applies and the overall logic of the rejection. Nor does Bell or Deuel issue a blanket prohibition against the application of methodology in rejecting product claimed defining DNA of cDNA. It is perfectly acceptable to consider the method by which a compound is made in evaluating the obviousness of the compound. In determining obviousness, it is appropriate to consider such matters as the manner of preparation of the composition vis-a-vis the prior art, the structural similarities as well as differences between the claimed composition and that of the prior art and the presence or absence of properties which would unobvious in view of the prior art. As noted in

In re Cofer, 354, F.2d 664, 148 USPO 268 (CCPA 1966), the particular structure or form of a chemical compound is an important consideration in determining obviousness under 35 USC 103; but it is not the only consideration.. A compound may well be defined or described by characteristics other than its chemical structure.

It would have been have been a matter of routine experimentation well within the ordinary skill level of art to generate chimeric or humanized LM609 antibodies, DNA encoding said antibodies, given the LM609 antibody and hybridoma and its associated properties known in the prior art. The instant claims are drawn to αvβ3-specific/ LM609-specific antibodies and fragments thereof and nucleic acids encoding said antibodies, particularly the LM609 specificity.

The primary references clearly teach αvβ3-specific antibodies the instant LM609 specificity and associated properties as valuable diagnostic and therapeutic tools in various biological processes. These references differ from the instant claims by not disclosing the generation of recombinant forms and nucleic acids of the LM609 antibody and hybridoma per se.

Given the availability of the LM609 antibody and hybridoma together with general immunoglobulin gene cloning and expression strategies, it would have been have been a matter of routine experimentation well within the ordinary skill level of art to generate chimeric or humanized LM609 antibodies, DNA encoding said antibodies. Given the highly conserved nature of immunoglobulin gene organization and structure and the availability of probes and PCR primers for immunoglobulin gene cloning, one of ordinary skill in the art could have isolated the functionally rearranged heavy and light chain variable regions from the LM609 hybridoma cell line and determined their sequences with a complete expectation of success. For example, the ordinary artisan does not need to determine the amino acid sequences of a rearranged V (variable) region before cloning. The claims do not differ unexpectedly or unobviously from what one of ordinary skill in the art would have expected to obtain given the known LM609 hybridoma thereof, the known heavy and light chain and the art known techniques regarding the production of chimeric antibodies, as acknowledged by the number of available art known procedures disclosed in the instant specification and cited on the Information Disclosure Statement. The claimed DNA sequences must encode a recombinant antibody comprising heavy and/or light chain variable regions of the LM609 antibody.

Immunoglobulin gene structure and organization were well understood in the art a the time the claimed invention was made and that strategies for cloning the DNAs encoding immunoglobulin variable regions genes were well established in the art at the time the claimed invention was made, as were methods for the production of DNA constructs encoding immunoglobulin variable regions. In addition, it was known at the time the invention was made that the benefits of producing recombinant antibodies to reduce the immunogenicity of therapeutic and diagnostic antibodies in human patients. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant has not provided any objective evidence to indicate that the resulting amino acid or nucleotide sequences were unobvious at the time the invention was made. As pointed out in the previous Office Action, it was noted that the instant disclosure relied upon standard humanization procedures to derive the claimed antibody and nucleic acid compositions. Also, it is noted that Biotechnology Newswatch (1/16/95 and 2/6/95) references above support the routine nature of providing an antibody/hybridoma of interest to a commercial interest to develop humanized antibodies and the nucleic acids encoding said antibodies by routineers in the art at the time the invention was made. Applicant argues that the claimed compositions are directed to LM609 grafted antibodies and nucleic acids encoding said antibodies in contrast to the prior art teachings of LM609 antibody. However, applicant's specification and arguments, filed in Paper No. 6, also indicate that "substantially the same" encompasses LM609 or LM609 grafted antibody. Given the breadth of the claims to read on the LM609 antibody, the instant antibodies and nucleic acids read on a genus of antibodies and nucleic acids encompassed by LM609 and modifications thereof.

Applicant's arguments are not found persuasive.

15. No claim is allowed.

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [lila.feisee@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Phillip Gambel, Ph.D.
Patent Examiner
Technology Center 1600
June 4, 1998

LILA FEISEE
SUPERVISORY PATENT EXAMINER